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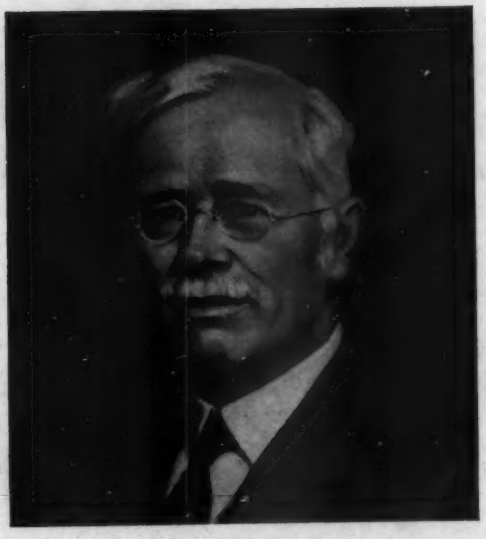
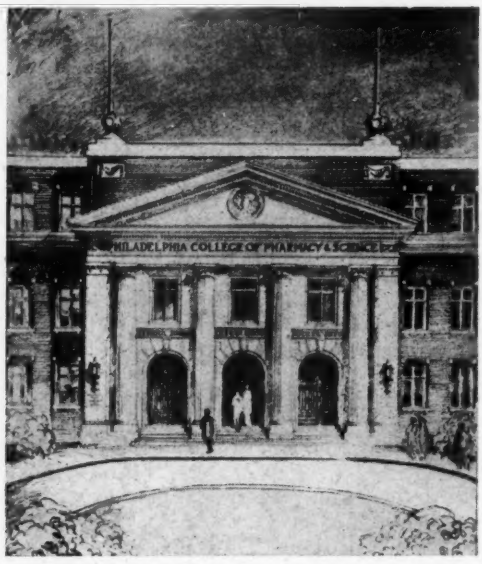


DR. EDWARD KREMERS

Teacher Scientist Historian

JULY
1941



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AMERICAN JOURNAL OF PHARMACY

AND THE SCIENCES SUPPORTING PUBLIC HEALTH

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OUR COVER

DR. EDWARD KREMERS

IN the profession of pharmacy, so replete with historical background and fact, historians are too few. The name of Dr. Edward Kremers and the history of pharmacy are almost synonymous, for from his pen have flowed many words about the traditions and past happenings in our noble art, and, most recently, he has edited and published, with his colleague, Dr. George Urdang, a most complete text entitled, "The History of Pharmacy".

Dr. Kremers was born in Milwaukee, Wisconsin, in 1865. His pharmaceutical education was obtained at the Philadelphia College of Pharmacy and at the University of Wisconsin, from which he graduated in 1886. He received the degree of Ph.D. from the University of Göttingen in 1890, and the University of Michigan and the Philadelphia College of Pharmacy and Science bestowed honorary degrees upon him at later dates.

From 1892 until 1935 he was director of the course in pharmacy at the University of Wisconsin and he directed the pharmaceutical experimental station there from 1912 until 1935. Since that time he has been Emeritus Director, devoting most of his efforts to his splendid compilation of historical facts printed by the J. B. Lippincott Company of Philadelphia.

Dr. Kremers' scientific accomplishments in plant chemistry, botany, pharmacognosy and teaching were outstanding at a time when work in these fields was of paramount importance to the progress of the profession.

For all of these achievements the American Journal of Pharmacy salutes him.

The dedication above was written before the editor learned of Dr. Kremers' death on July 9. We shall miss him and his passing saddens the entire profession of pharmacy.

EDITORIAL

A MISCARRIAGE OF JUSTICE?

● On this page the editor offers for your consideration his opinion on important events in the field of pharmacy.

THE action of the Department of Justice in bringing suit against the three manufacturers of insulin for price fixing in violation of the Sherman Act is another example of the commonly observed failure of one group of experts to properly evaluate conditions in a field foreign to that in which they are specifically trained. We have numerous examples of this lack of understanding frequently observed in everyday life. Thus the lawyer feels that he is robbed when a surgeon sends him a bill for professional services and the physician in return considers exorbitant the fee for drawing up his "last will and testament" in proper legal form.

Were there not so many flagrant cases in our national life demanding anti-trust prosecution this action would not by comparison seem quite so unwarranted. We cannot help but feel that this suit by the Department is explained by judging the issue entirely on outward appearances rather than by a careful approach to the matter, including an investigation as to the reasons for uniform prices.

The sincerity of the Department of Justice is not questioned in their whole-hearted efforts to properly enforce the Sherman Act. The price fixing of any product by an industry is unquestionably improper, but in the case of insulin the uniformity of price was attributable to other causes. Since each company's product was *identical,* the market price was invariably established by that company which could produce it at the least cost. Competitors were forced either to match this price immediately or discontinue selling the product.

The control of insulin at present actually originates outside the United States. In 1925 the University of Toronto acquired patents which enabled them to control rigidly every phase of insulin production. Some persons may question the wisdom of an educational institution's obtaining such patent rights, but let it be noted that the exercise of these patents has been most commendable. Not only has the revenue derived from them been used to support an extensive

research program, but by this means there has been guaranteed the close supervision of a potent product, the uncontrolled manufacture and sale of which, if permitted, would have led to chaos. It must be remembered that at the time insulin was introduced we had no effective food and drug legislation as at present, and we feel that the University of Toronto had a public responsibility that it could not at that time discharge by any other method than the one chosen.

The manufacturers in this country have also felt that responsibility. In no field of medication has there been more expensive and painstaking research—research that has led to great advances in improving the purity of the product, developing new and better dosage forms and placing their use on a sound, safe basis. Concomitant therewith has been a steady reduction in the cost to the consumer. In fact, the present cost of insulin to the consumer is now less than one-fourth that in 1925. On the other hand, the cost of material for insulin production is higher than it was in 1925. Does this sound like the record of a group who were motivated solely by profit? The truth of the matter is that a fourth manufacturer recently suspended insulin production because the operation was unprofitable, and two out of the three present manufacturers have stated that they were selling the product at a loss.

Of course one may argue that in pleading *nolo contendere* the defendants admitted their guilt, but sight should not be lost of the practical considerations involved. To properly defend themselves and set before the courts the *whole* truth would have cost a tremendous figure and, in addition, certain of the indispensable personnel of these companies would have been required to give up many weeks of valuable time which now, during the national emergency, would seriously impair the production of sorely needed supplies. The lesser of the two evils was indeed the sensible and patriotic course, but let no one assume that, had it been feasible to defend this case, the result would have been the same.

There are today great opportunities in certain areas of pharmacy for governmental action to effect a "housecleaning", but we do feel that in this instance a hardship has been applied and a certain unwarranted stigma attached to a group who have tried to be fair to all concerned and yet have been the unfortunate victims of circumstance.

L. F. Tice.

THE CHEMISTRY OF SOME OF THE NEWER DRUGS

By Arthur Osol

Alpha-Tocopherol

Vitamin E

5, 7, 8-Trimethyltocol

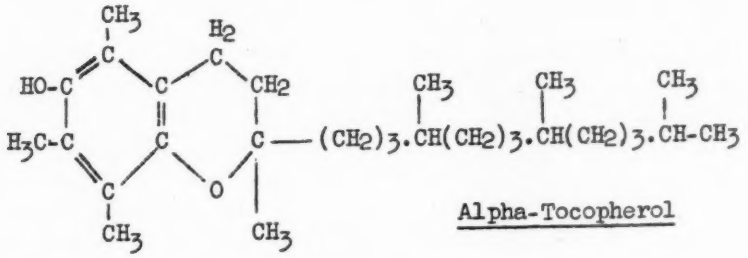
EVANS and Bishop, in 1922, reported on the existence of a dietary substance essential for normal reproduction in the female rat. Addition of wheat germ oil to the diet was shown to correct the condition and the lacking essential present in the oil was designated Vitamin E.

Efforts to separate the vitamin led, in 1936, to the isolation from wheat germ and other oils of three substances designated, respectively, alpha-tocopherol, beta-tocopherol, and gamma-tocopherol. Of these, alpha-tocopherol was shown to be the most effective biologically. Its structure has been definitely established and an identical compound synthesized.

A number of other compounds have been shown to have vitamin E activity, some of these having a much simpler structure than the tocopherols, but none having greater biological activity than alpha-tocopherol.

The medicinals for which chemical data are given here have been selected on the basis of established clinical value or extensive experimental usage. Obviously, this listing of new medicinals is not complete; it does include, however, some of the more important compounds not discussed in previous seminar lectures or which have recently been introduced.

Alpha-tocopherol can be prepared synthetically by several methods; one procedure utilizes trimethylhydroquinone and phytol (an alcohol obtained from the decomposition of chlorophyll) as starting compounds. The structural formula of alpha-tocopherol is:



Alpha-Tocopherol

Alpha-tocopherol is a light yellow, very viscous, oily liquid. It is odorless and has an insipid taste. It has a specific gravity of about 0.95 at 25° C., is practically insoluble in water but soluble in most organic solvents. With 95 per cent. ethyl alcohol it is miscible in all proportions but is soluble only to the extent of about 10 per cent. in 85 per cent. alcohol. It is miscible in all proportions with peanut and with sesame oil and such solutions may be sterilized at 120° C. for twenty minutes. Alpha-tocopherol is oxidized by atmospheric oxygen and by oxidizing agents and deteriorates on exposure to light. Tablets or capsule mixtures should contain a neutral adsorbent such as tribasic calcium phosphate, along with starch and some sugar as a reducing agent. Sugar coating of tablets is desirable in order to protect the tocopherol from action of air and light.

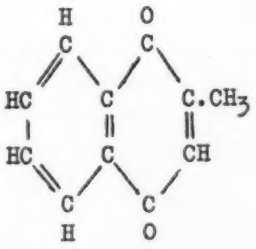
2-Methyl-Naphthoquinone

(Vitamin K Active)

Noting the development of hemorrhages in the skin and mucous membranes of chicks maintained on a fat-free diet Dam, in 1929, showed that the hemorrhagic tendency appeared to be the result of a decrease in the prothrombin content of the blood. As the condition was corrected by adding to the diet spinach, alfalfa and the like, Dam believed the then unidentified antihemorrhagic principle to be vitamin-like in nature and accordingly designated it vitamin K (after Koagulations-Vitamin).

In 1939, the isolation of two substances having vitamin K activity was announced. The first of these, obtained from alfalfa, was denominated vitamin K_1; the second, isolated from putrefied fish meal, was called vitamin K_2. Both principles were shown to be naphthoquinone derivatives, vitamin K_1 having been recently identified as 2-methyl-3-phytyl-1, 4-naphthoquinone, and also synthesized.

Subsequent researches showed that many simple naphthoquinones have vitamin K activity. Of the naphthoquinones thus far investigated, 2-methyl-1, 4- naphthoquinone appears to be the most potent agent employed clinically. The activity of 2-methyl-1, 4-naphthoquinone is reported to be approximately three times that of vitamin K_1. By virtue of its ready availability, this substance was proposed by Doisy, Thayer and associates as a standard reference material for determinations of vitamin K activity. Its structural formula follows:



2-Methyl-Naphthoquinone

2-Methyl-1,4-naphthoquinone is a yellow crystalline powder, having practically no odor and melting at 106°-107° C. It dissolves in water to the extent of 10 mgm. in 100 cc. at room temperature (the solution being prepared by warming); in 95 per cent. alcohol 1.7 gm. dissolve in 100 cc. at room temperature; in sesame oil 1.3 gm. dissolve in 100 cc. at 27° C. Aqueous solubility is not affected by acids; alkalis decompose the substance.

Sesame oil solutions containing 1 mgm. per cc. (a commonly used form of administration) may be sterilized by autoclaving in sealed ampuls if protected from light. 2-Methyl-1,4-naphthoquinone is stable in air when protected from light. The substance is incompatible with reducing agents, halogens and alkalis.

Chemical addition of a molecule of $NaHSO_3$ to the compound produces 2-methyl-1,4-naphthoquinone-3-sodium sulfonate, which is water soluble.

Nicotinic Acid

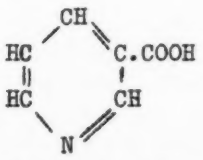
Beta-Pyridinecarboxylic Acid, P-P Factor

Nicotinic Acid Amide

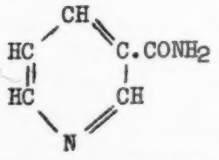
Nicotinamide

First prepared in 1867, nicotinic acid was not isolated from biological material until 1912, and only in 1937 was its importance as a nutritional element recognized. In the latter year, Elvehjem and his associates reported the cure of canine blacktongue by nicotinic acid and also the occurrence of nicotinic acid amide in liver, from which they isolated it. Widespread use of nicotinic acid in the treatment of pellagra followed Elvehjem's report, with effective results. At present it is believed that nicotinic acid, its amide, or some substance derived from it physiologically, is the pellagra preventive vitamin, or is probably the most important factor if clinical pellagra is a multiple vitamin deficiency.

Nicotinic acid, sodium nicotinate and nicotinic acid amide are all used in the treatment of pellagra. The amide appears to have an advantage over the other compounds in that such reactions as cutaneous flushing, gastric distress and sensation of warmth, which are commonly encountered following nicotinic acid administration, are obviated.



Nicotinic Acid



Nicotinic Acid Amide

Nicotinic acid occurs as a white, crystalline powder, melting between 235° and 237° C. 1.67 gm. dissolve in 100 cc. of water at 25° C.; it is freely soluble in alcohol and in solutions of alkali carbonates and hydroxides. Aqueous solutions are not decomposed by autoclaving at 120° C. Sodium nicotinate solutions may be prepared by neutralizing a saturated solution of nicotinic acid with sodium bicarbonate, using phenolsulfonphthalein as indicator, then diluting the solution as required. The sodium salt is also obtainable as white crystals or crystalline powder, stable in air and having the following solubilities per gram of salt: in about 1.4 cc. of water, in about 60 cc.

of alcohol, in 10 cc. of glycerin. Aqueous solutions of sodium nicotinate have a pH of about 7.

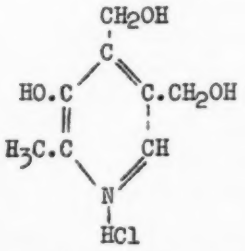
Nicotinic acid amide occurs as a white, slightly deliquescent, crystalline powder, melting between 129° and 131° C. One gram of it dissolves in 1 cc. of water, in 1.5 cc. of alcohol and in 10 cc. of glycerin. The aqueous solution is practically neutral in reaction.

Pyridoxine Hydrochloride

Vitamin B_6 Hydrochloride

Vitamin B_6 was first established as a component of the vitamin B complex in 1935 by György, who found that its deficiency caused a characteristic dermatitis in rats. Subsequently it was isolated from natural sources in laboratories in the United States, Germany and Japan, and, in 1939, its synthesis was reported almost simultaneously by several workers.

Chemically, the vitamin is a derivative of pyridine, but it is synthesized by a reaction between ethoxyacetylacetone and cyanoacetamide. Among the recognized natural sources of vitamin B_6 are rice, bran, liver, yeast, legumes, egg yolk, cereals and seeds. Fish and meat are said to contain small quantities of the vitamin. The formula of vitamin B_6 hydrochloride is:



Pyridoxine Hydrochloride

In the form of its hydrochloride, vitamin B_6 occurs as a white, odorless crystalline powder having a saline taste. It has a melting point between 206°-208° C.; is soluble in water to the extent of 22 grams in 100 cc.; in alcohol 1.1 grams dissolve in 100 cc. at 25° C. In solid form vitamin B_6 hydrochloride is reasonably stable to daylight and to air. It is also reasonably stable in solutions having a pH below 5; in solutions of pH greater than 6 it decomposes, rapidly so when the solutions are heated. The pH of aqueous solutions of vitamin B_6 hydrochloride is about 3. The substance is oxidized by

strong oxidizing agents and its aqueous solutions are colored red by ferric salts.

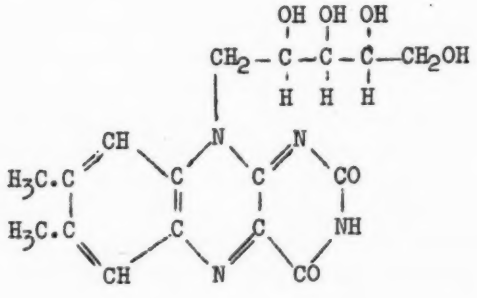
Too short a time has elapsed since the identification and synthesis of the vitamin to permit adequate investigation of its therapeutic usefulness. Current reports indicate that this vitamin may be of value in treating patients afflicted with pellagra, whose symptoms do not evidence response to administration of other factors of the B complex. Other diseases in which vitamin B_6 has produced improvement are cheilosis, pseudohypertrophic muscular distrophy, Parkinson's syndrome and certain types of anemia. However, much more clinical study must be completed before definite conclusions can be drawn concerning the effect of this vitamin in the treatment of various diseases.

Vitamin B_6 hydrochloride is now available on the market as a powder, in tablets containing 1 mgm. and 25 mgm. of the vitamin, and in ampuls containing 50 mgm. in 1 cc. of aqueous solution.

Riboflavin

Vitamin B_2, Vitamin G, Lactoflavin

In 1933, three different laboratories almost simultaneously called attention to the probable identity of certain fluorescing pigments, found in whey and other natural products, with vitamin G or vitamin B_2. Eventual isolation of the flavins, as the pigments are called, led to the finding that they are closely related, and that the flavin synthesized from d-ribose and dimethylisoalloxazine possessed the greatest vitamin B_2 activity. Subsequently, the Council on Pharmacy and Chemistry suggested the name riboflavin as a substitute for vitamin G and vitamin B_2. The structural formula for riboflavin is as follows:



Riboflavin

Riboflavin occurs as an odorless or practically odorless, orange-yellow, fine crystalline powder, melting at 280° C. with decomposition. *Protected from light* it is stable at ordinary temperatures. In solution riboflavin decomposes under the influence of visible or ultraviolet light, the chain of reactions depending upon pH, presence or absence of oxygen, intensity of illumination, temperature, etc. In the dark, acidified solutions of riboflavin are stable. For example, a solution at a pH not above 6.5 may be kept at a temperature of 100° C. in the dark for an hour without appreciable decomposition.

At 27.5° C., 12 mgm. of the vitamin dissolve in 100 cc. of water, producing a solution having a strong yellow-green fluorescence. Some evidence indicates that considerably more vitamin may be dissolved by heating the water, without subsequent crystallization of the solute. This finding will require further investigation, however. In alcohol, but 4.5 mgm. of the vitamin dissolve in 100 cc. at 27.5° C.

Riboflavin is quite stable to oxidizing agents, including hydrogen peroxide, bromine water and concentrated nitric acid. It is reduced by many reducing agents, however.

Magnesium Trisilicate

Mutch, in 1936, showed that hydrated silicates of magnesium possess antacid and adsorbent properties which are developed to a maximum in the trisilicates but which become negligible in the tetrasilicates or talcs. A synthetic trisilicate, $Mg_2Si_3O_8.nH_2O$, approximating in composition to the chemical formula of sepiolite or meerschaum, was found to be far more active as an adsorbent and antacid than any of the other silicates which were examined.

According to Mutch, the antacid property of magnesium trisilicate results from the following reaction:

$$Mg_2Si_3O_8.nH_2O + 4HCl \rightarrow 2MgCl_2 + 3SiO_2 + (n+2)H_2O$$

Mann, however, believes that the hydrated silicic acid which is produced in the foregoing reaction acts as an adsorbent for hydrochloric acid, thus enhancing the therapeutic effectiveness of magnesium trisilicate in reducing gastric acidity. Whatever may be the complete mechanism of reduction of gastric acidity, the rate of neutralization or removal of acid progresses slowly, about four hours being required for the attainment of equilibrium. In four hours, and at body temperature, a gram of trisilicate will neutralize about 225 cc. of hydrochloric acid of the concentration present in the stomach. It is this

slowness of reaction which gives an important advantage to magnesium trisilicate. The period of useful antacid action is approximately equal to the time required for gastric digestion, and to the usual interval between meals.

Because of its insolubility it is impossible to produce alkalosis by giving large doses of magnesium trisilicate. Moreover, the magnesium chloride which is produced when magnesium trisilicate reacts with hydrochloric acid is converted to magnesium hydroxide in the intestines, thus preventing any interference with the internal balance of bases and acids.

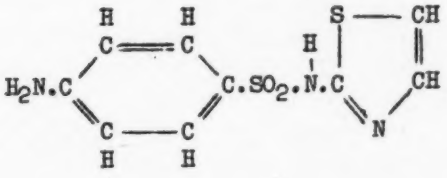
In addition to its important property of reacting chemically with hydrochloric acid, magnesium trisilicate is also a powerful adsorbent, just as is the hydrated silicic acid produced by the interaction of trisilicate and acid. When tested with methylene blue, magnesium trisilicate shows an adsorbent power greatly superior to the bismuth salts, magnesia, aluminum hydroxide, prepared chalk, kaolin and other similar medicaments. Among the substances which can be adsorbed are acid and basic dyes, alkaloids, bacterial toxins, putrefactive amines such as histaminase, and food poisons such as mussel poison and muscarine. Pepsin, too, is adsorbed but it is claimed by Mutch that it is still available for the purposes of digestion.

To be satisfactory for therapeutic use, the synthetic trisilicate must be precipitated under such conditions as will yield a product having pronounced acid-combining and adsorptive powers. To define the quality of the product, laboratory control analyses must include such tests as of acid combining power and of adsorptive power.

Sulfathiazole

2-Sulfanilylaminothiazole

This important chemotherapeutic substance is another in the rapidly growing series of sulfonamide compounds, being the thiazole analogue of sulfapyridine. It differs from sulfanilamide in that a hydrogen atom of the amide group is replaced by the thiazole group.



Sulfathiazole

Sulfathiazole now appears to be established as being superior to sulfapyridine in the treatment of certain staphylococcic infections, and about as effective as the latter drug in pneumococcal infections. Advantages claimed for sulfathiazole, in comparison with sulfapyridine, are (1) less tendency to cause serious nausea or to provoke vomiting, and (2) lower toxicity.

Sulfathiazole is a white, crystalline powder melting between 200° and 202° C. At 26° C. it is soluble in water to the extent of 60 mgm. in 100 cc. and in alcohol, 525 mgm. per 100 cc. The saturated aqueous solution is reported to have a pH of 6.0.

To be therapeutically effective, the concentration of free thiazole in the blood should be 3 to 6 mgm. per cent. This necessitates the determination, at least once daily, of the sulfathiazole content of the blood in order to adjust dosage of the drug. Several relatively simple tests for the determination of free sulfathiazole are available and may be readily performed by one having had some experience with the procedures of clinical chemistry.

Sulfathiazole is also available in the form of sulfathiazole sodium sesquihydrate, a water-soluble form suitable for intravenous injection where prompt chemotherapeutic effect is necessary as a life saving measure. Solutions should be prepared only immediately before use and must not be heated, for the substance is unstable. Sterile ampuls containing the dry powder are available.

Zinc Peroxide

Because of its astringent and disinfecting properties, zinc peroxide has long found use in the treatment of certain dermatoses and of infected wounds. Meleny found that the regular grade of zinc peroxide on the market was generally not suitable for the control of certain types of infection. Accordingly, the duPont Research Laboratories developed a special grade of zinc peroxide (ZnO_2), having particular physical and chemical specifications, which proved to be satisfactory for medicinal use.

This medicinal grade of zinc peroxide is supplied as a dry powder. Before use it must be sterilized, in small quantities, by heating in a dry oven for four hours at exactly 140° C. Lower temperatures are reported to be not effective in this procedure, which is in part an activation of the peroxide. Higher temperatures result in decomposition of the compound. After sterilization the peroxide may be

used for several weeks but it begins to deteriorate slowly after a month's time. It should not be sterilized more than once.

For use, the sterilized powder is placed in a sterile basin, and enough sterile distilled water is added to produce a uniform, creamy suspension of about the consistency of heavy cream. The suspension is then applied to the wound and the latter dressed appropriately.

It is suggested that the following test be applied to determine the effectiveness of zinc peroxide: About 5 gm. of powder is suspended in 100 cc. of distilled water. The effective material sediments in about thirty minutes, leaving a clear supernatant fluid. In the course of an hour, bubbles of oxygen appear in the sediment and produce a bulky curd-like mass, penetrated with the small bubbles of oxygen. In twenty-four hours this amount of zinc peroxide produces from 10 to 12 cc. of oxygen at room temperature. Favorable results cannot be expected from material which does not conform to this test. The ineffective material sediments slowly, giving a milky appearance. This material remains packed at the bottom of the container and shows little sign of oxygen production, as evidenced by absence of bubbles.

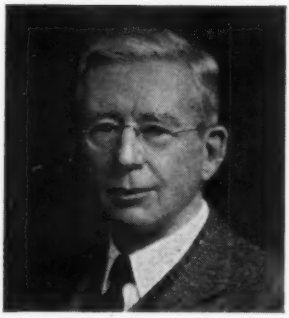
This and the article by H. C. Wood beginning on page 273 are based on lectures presented at the Third Annual Seminar on Modern Pharmaceutical Practice of the Philadelphia College of Pharmacy and Science, January 27-29, 1941.

Sulfadiazine Gives Good Clinical Results

In the June 14th issue of the Journal of the American Medical Association a paper by Finland, Strauss and Peterson reports their results of treating 446 patients with sulfadiazine. Among the diseases treated were pneumococcic, staphylococcic and streptococcic pneumonias, acute infections of the upper respiratory tract, erysipelas, acute infections of the urinary tract and meningitis. They found it to be quite effective and most important of all, considerably less toxic than sulfathiazole and sulfapyridine.

THERAPEUTICS OF SOME NEW DRUGS

By Horatio C. Wood



WHEN the vitamin idea was new we used to talk of "fat soluble A" and "water-soluble B". Now they have broken up vitamin B into a dozen pieces. But the original idea is still a good one because all of them, B1, 2, 3, 4, etc., are closely related physiologically, although not chemically. The two outstanding deficiency diseases in this group are beri-beri and pellagra. We say beri-beri is due to a lack of thiamine and pellagra to a lack of nicotinic acid, but in both of them the conditions are complicated by deficiency of many of the other substances belonging to this group. In certain diets the inadequacy of one factor will be the more marked, in another improper diet the lack may be greatest for another element and the symptoms will be more or less different. But in the treatment of either beri-beri or pellagra it has been found that in many cases complete cure is not accomplished until other fractions of the B group are added.

All of the B group are constituent parts of the structure of one or another of the enzymes by which the body cells are able to liberate the energy stored in the food materials brought to them by the blood. Most of these enzymic actions involve a team-work between two catalysts, which are then called coenzymes; for example, an oxidase may require the cooperation of a hydrogenase.

Neither outspoken beri-beri nor pellagra are common in this part of the world but there are a considerable number of persons whose health is below normal because of scantiness in their intake of one or another of the various numbers of the B group. These conditions are spoken of as "subclinical" avitaminoses.

Thiamine

While frank pellagra is a rare condition in this section of the United States, inadequate amounts of thiamine in the diet of Phila-

delphians is probably more common than of any other vitamin. The reason for this is that there is no single food which is outstandingly rich in thiamine. The most important source of thiamine, in our ordinary diet, is wheat; and in the present methods of milling flour most of this vitamin is removed. Whole wheat bread contains nearly 2.0 milligrams of thiamine per pound, ordinary white bread only about 0.250 milligram. We need between 1 and 2 milligrams per day. The average consumption of wheat flour in this country is nearly 9 ounces a day. If we ate whole wheat bread this would yield us about one milligram of thiamine; white breads gives us only 0.13 milligrams per day. An effort is at present being made to popularize the use of bread which has been artificially enriched with thiamine but it has not yet perceptibly changed the food habits of the masses.

Among the symptoms due to scarcity of thiamine intake are: failure of appetite, sluggishness of the alimentary tract and vague pains suggestive of mild peripheral neuritis, often associated with evidence of subnormal functioning of the central nervous system such as irritability, abnormal fatigability or general lassitude.

Thiamine is apparently an essential part of the cocarboxylase whose function is to break down pyruvic acid, which is an intermediate product in the carbohydrate metabolism.

Because one of the most striking symptoms of beri-beri is peripheral neuritis physicians have wondered whether an excess of vitamin might be useful in the treatment of nerve disorders even when there is no evidence of an avitaminosis, and are using the drug experimentally in the treatment of all sorts of neuritic pains and as a sort of general nerve tonic. It is also being tried in various alimentary conditions, especially anorexia. Because there has been some evidence of connection between thiamine deprivation and the endocrine system it has also been employed in diabetes and hyperthyroidism. Whether or not an excessive thiamine intake is actually beneficial in these cases is not yet established, but at least we can say that it does no harm.

One point needs to be emphasized in connection with the therapeutic use of all vitamins, that is the difference between the medicinal dose and the food dose. It takes much less to keep us well than it does to make us well. The requirements of thiamine are on the average about one or two milligrams a day but to produce a thera-

peutic result it is usually necessary to administer eight or ten times this amount.

Other Factors of B Complex

The outstanding symptoms of pellagra are in three groups: disturbance of intellection, varying from mild hebetude to severe disorientation and sometimes even almost complete coma; severe inflammations of the tongue, mouth and skin; and frequently diarrhea. While the subclinical pellagrous symptoms have not attracted as much attention as have the thiamine deficiencies, yet there is evidence that they do occur, especially in alcoholics, even in this part of the world. As the effects of large doses of nicotinic acid are distinctly unpleasant physicians have not experimented with it as freely as with the other vitamins.

The average human requirement of nicotinic acid is somewhere in the neighborhood of 20 or 30 milligrams a day, but in severe pellagra as much as 500 milligrams a day have been administered.

Riboflavin and pantothenic acid have been definitely established as being essential to a large variety of the lower forms of life including bacteria, molluscs and rats. But our knowledge of their part in human disease is still very scanty. Cases of pellagra have been reported in which nicotinic acid, although causing marked amelioration of symptoms, failed to produce complete cure but in which the addition of riboflavin led to rapid recovery. In one series of experiments on humans a diet completely lacking only in riboflavin gave rise to a rather well defined syndrome—marked by a peculiar inflammatory condition of the lips and eyes—which promptly subsided under the addition of riboflavin. The daily requirements of riboflavin have been, rather uncertainly, estimated as around two or three milligrams a day.

Pyridoxin has been experimented with in various muscular dystrophies and anemia, but the results have not been conclusive. The medicinal dose of either is usually given as about 50 milligrams a day.

As far as I know pantothenic acid, as such, has not been used in any diseased conditions in man except as an adjunct in pellagra. There is some reason to believe that pantothenic acid is functionally closely associated with riboflavin.

Naphthoquinones

The coagulation of the blood depends on the changing of a soluble protein, called fibrinogen, by action of the enzyme thrombin, into an insoluble protein. The fibrinogen is always in the blood. Thrombin does not exist in the blood, otherwise we would get clotting in the blood vessels. There is, however, in the blood stream a material known as prothrombin (or thrombinogen). This substance reacts with a material, found in practically all the body tissues except the blood—which was formerly called cephalin but is now usually known as thromboplastin or thrombokinase—in the presence of calcium, to form the active enzyme. The chain of reactions in the clotting of blood may therefor be written: prothrombin + thromboplastin + calcium + fibrinogen = fibrin. Take away any link from this chain and the blood will not clot. Delayed clotting may be due to deficiency of any one of these factors. One of the frequent accidents which has long been a source of worry to surgeons operating in cases of gall-stones is the liability of patients to dangerous hemorrhage. Although much had been written and various theories proposed to explain this tendency to hemorrhage in patients suffering with diseases of the liver it was not until 1929 that Dr. Dam of Copenhagen, engaged in some vitamin research, accidentally stumbled over the key to the conundrum. He found that newly hatched chicks on a certain experimental diet became liable to hemorrhage and that this tendency could be overcome by feeding them with spinach or alfalfa. Later he showed that the hemorrhagic condition was due to a decrease of prothrombin in the blood of these chicks. He, therefore, postulated a new vitamin which he called vitamin K (from the Danish Koagulation). Later it was found that there were a variety of other substances which could take the place of alfalfa or spinach. All of these substances which enable the body to manufacture prothrombin are derivatives of naphthoquinone.

Newly born babies take almost no food the first two days. The store of vitamin K with which they come into the world is not always sufficient to carry them over this period and not infrequently they develop a condition known as hemorrhagica neonatorum. The interesting thing about this condition is why all babies are not afflicted. The explanation commonly believed today is that if bacteria be in the intestinal tract these microorganisms may manufacture enough

of this vitamin to protect the infant until he begins to ingest it with his food.

The cause of the hemorrhagic tendency in jaundiced patients probably depends largely on the fact that the natural vitamin is scarcely soluble in water and requires the presence of bile in the intestines to promote its absorption. This is not the whole story, however. It must be remembered that these naphthoquinones are not prothrombin. They are one of the building materials which the body requires to make prothrombin. The prothrombin itself is manufactured in the liver and in cases of severe injury to the liver, such as acute hepatitis or cirrhosis of the liver, this organ may not be capable of fulfilling its function. It should be pointed out in this connection that the naphthoqinones are not a cure-all for hemorrhagic conditions. It is of no service in hemophilia—that dreaded inheritance of the Hapsburg's—nor in hemorrhages due to snake-venom, scurvy, or deficiency of calcium. It is only useful when the non-coagulability of the blood is the result of lack of prothrombin.

Tocopherols

In 1922 Evans reported that with a certain restriction of diet, female rats which were apparently in perfect health failed to bear living offspring; they might become pregnant, but the embryo died at an early stage in the gestation. This condition could be corrected by adding wheat-germ oil to the diet. Shortly after, it was found that male rats on a like diet were unable to fertilize normal females. The ostensible lacking vitamin was called "vitamin E" and has since received much popular notoriety under the name of "antisterility vitamin". It is as yet uncertain whether this vitamin is essential for other species of animals, although there is evidence that it affects the hatchability of hen's eggs.

Somewhat later an entirely different group of conditions were reported as occurring in rats who were fed on a diet completely lacking in tocopherols. These animals developed degenerative changes in both the muscular system and the anterior horns of the spinal cord. The similarity of the symptoms and pathologic lesions in these rats to certain nervous diseases of men has led to the experimental use of the tocopherols in the treatment of a number of heretofore hopeless forms of progressive paralysis. Early reports of its effects in such incurable diseases as myasthenia gravis and psuedo-

hypertrophic muscular dystrophy and in the spinal cord degenerations following untreated pernicious anemia gave rise to the hope that a useful method of treatment had been found for these hitherto incurable disease. But the most recent reports have been rather disappointing. It has been suggested that the two fractions in wheat germ oil, alpha- and beta-tocopherol, may have different functions; that the former may be the antisterility factor and the beta-tocopherol the one essential for maintenance of muscular health. The dose of the tocopherols which has been employed is usually in the neighborhood of 50 to 100 milligrams a day.

Gastric Antacids

It is said 75 per cent. of cases called dyspepsia are associated with an increased acidity of the stomach. This fact explains the tremendous use of sodium bicarbonate by the physician, the patent-medicine vender and the self-prescribing patient. Sodium bicarbonate, however, has certain objectionable features. In the first place while its action is quick, it is also quickly over. Secondly, there is reason to believe that if the stomach contents become actually alkaline this alkalinity tends to excite secretion of hydrochloric acid. Thirdly, there is a considerable amount of carbon dioxide given off in the reaction between the bicarbonate and the acid; fifteen grains of sodium bicarbonate will liberate approximately one pint of carbon dioxide. Fourthly, if taken in large doses there is likely to be an absorption of the salt into the general circulation with consequent possible disturbances of the saline balance in the blood. Calcium carbonate is decidedly less objectionable from many standpoints than the sodium salt but still has the disadvantage of evolving gas. Magnesia does not evolve gas but it is more alkalizing in its effects than either of the aforementioned drugs. Recently a number of gastric antacids have been brought forward as offering advantages over these older neutralizers.

The Pharmacopœial Supplement has recognized the tribasic calcium phosphate which was previously official in the National Formulary. This salt is so nearly insoluble that its solutions are practically neutral and therefore it cannot render the gastric contents alkaline. It evolves no gas; it is very slowly absorbed and hence cannot greatly disturb the saline balance in the blood. Its neutralizing effect goes on very slowly, in fact for many conditions too slowly.

Magnesium triphosphate has much the same advantages as the calcium salt but that it has any great superiority to it does not seem to me very obvious.

A very interesting compound is the magnesium trisilicate. In the case of the calcium or magnesium triphosphate the neutralizing effects depend upon the power of these salts to combine the hydrogen ion into a non-active form. Magnesium silicate has this same property but after the combination with hydrochloric acid we have as a result of the reaction, magnesium chloride and a dihydroxid magnesium silicate in a colloidal form. The latter has the power of adsorbing hydrogen ions and thus neutralizing acidity, but as this silicate is feebly acid it is impossible to raise the pH even up to the point of neutrality. Therefore, by the use of this antacid we completely avoid the danger of stimulating secretion of hydrochloric acid. It is especially valuable in cases of so-called "peptic ulcers" whether in the stomach or duodenum. In these cases it is desirable to maintain the gastric secretions at a point very close to neutrality, without actually going over to the alkaline side, over long periods of time. This is accomplished probably as well by certain forms of magnesium silicate as any drug we have. The chief objection to magnesium silicate is the wide variety of kinds of magnesium silicate we have on the market. The various commercial preparations differ greatly in their chemical composition and in their neutralizing powers. An official standard for this drug is greatly to be desired and until we have such a standard available one cannot assign an accurate dosage for the commercial magnesium silicates.

Aluminum hydroxide is so nearly insoluble (about one and a half parts per million) that, despite its containing the hydroxyl ion, the solutions are practically neutral. For the same reason it has very little alkalizing effect. Aluminum hydroxide was formerly official in the Pharmacopœia, being used chiefly for its protective effect either in skin diseases or gastrointestinal irritations. The aluminum hydroxide of the U. S. P. IX had practically no neutralizing action. In recent years there have appeared preparations in which this salt was in colloidal condition and which have adsorbent properties analogous to those of activated charcoal. The most popular of these products are in the form of a gel. There is not yet sufficient evidence to allow a definite conclusion as to whether alumi-

num hydroxide gel has any advantage, aside from its color, over activated charcoal.

Sulfanilamide Derivatives

The discovery of the curative effects of sulfanilamide in streptococcus infections is undoubtedly the most important therapeutic discovery since that of arsphenamine. The importance of this discovery lies not merely in the fact that we now have a life-saving remedy for some highly fatal diseases, but pre-eminently because it has opened the door of hope for the conquest of the group of bacterial diseases for which antitoxins have been unavailable. It has been found that sulfanilamide itself is of more or less service against a number of species of pathogenic bacteria but in none of them has its curative powers been so striking as against the streptococci.

Of the various modifications of sulfanilamide which have been brought forward in the last eight years, the first of any real importance was sulfapyridine. Sulfanilamide is highly antagonistic to the streptococci, moderately antagonistic to pneumococci, practically inert against staphylococci; sulfapyridine is much more efficacious against pneumococci, but not so useful against streptococci, and is also feebly antagonistic to staphylococci. While the curative value of sulfapyridine in pneumonia is very potent it has one serious danger which does not occur with sulfanilamide. Both of these drugs form acetyl compounds in the body; the acetyl-sulfapyridine is so insoluble that it is precipitated in the kidneys and may block the ducts of the kidneys and cause complete cessation of the flow of the urine, which of course means the death of the patient unless the obstruction can be removed.

The second of the important offsprings of sulfanilamide is sulfathiazole. Its outstanding therapeutic property as compared to its predecessors is its high degree of efficiency against the staphylococci. The latter species of bacteria are of great pathologic importance as the usual germs of carbuncles and boils and frequently enter the blood stream and cause general septicemia. Against the pneumococci sulfathiazole seems perhaps a shade less efficient than sulfapyridine but decidedly superior to sulfanilamide. However, in pneumonia it is frequently given the preference over sulfapyridine because of a less marked, though not entirely absent, tendency to obstruct the kidneys.

PRELIMINARY CHEMICAL AND PHARMACOLOGICAL STUDIES ON "CUNDEAMOR," MOMORDICA CHARANTIA L. (PART I).

Cundeamor is a drug used empirically in Puerto Rico for the treatment of Diabetes Mellitus. This paper is part of a thesis presented to the Graduate School of the Philadelphia College of Pharmacy and Science, in partial fulfillment of the requirements for the degree of Doctor of Science in Pharmacy.

By Gilberto Rivera

Introduction

WITH the rapid development of synthetic chemistry, especially during the last decade, there has been a noticeable diminution in the pharmacological and chemical studies of plants, particularly those of tropical origin, which have a definite, though empirically established, usage in the treatment of certain diseases.

Among the Puerto Rican plants in this category are Bruja (*Bryophyllum pinnatum*), used in the treatment of acute nephritis; Coqui (*Cyperus rotundus*), administered to patients with calculii of the kidneys; Cohitre Morado (*Callisia monandra*), employed in treating chronic ulcers of the stomach, and Violeta (*Viola odorata*), applied in the treatment of mild cancer of the stomach. Caimito (*Chrysophyllum cainito L.*), Correguela (*Polygonum aviculare*), Mirtillo (*Vaccinium myrtillus*), Morera Negra (*Morus nigra*) and Cundeamor (*Momordica charantia L.*) are used in the treatment of diabetes mellitus.

In 1937 Dr. Asenjo, of the staff of the Department of Chemistry of the Puerto Rico School of Tropical Medicine, started a bibliographical study of such medicinal plants. This work was of such interest that the Guggenheim Memorial Association granted him a fellowship to carry on further research at the University of Wisconsin on *Cyperus rotundus, Ficus pumilla* and pineapple.

Asenjo (1) verified the work of Robins and Walti on *Ficus pumilla* and proved that the enzyme ficin was responsible for the

digestion of parasites in the human intestine. Later he established that fresh pineapple juice, *in vitro,* through its content of bromelin, was able to digest *Ascaris lumbricoides* and *Macracanthorynchus hirundinaceus,* thus proving that there is some scientific basis for use of the juice as an anthelmintic.

In his thesis presented to the University of Wisconsin (February, 1940), he also reports on the isolation of a substance from *Cyperus rotundus,* which is capable of dissolving several times its weight of lecithin and other amino acid substances associated with formation of calculi.

M. F. Daels made a few observations on the hypoglycemic properties of *Polygonum aviculare* in diabetic patients and recommended its use.

Dr. Rathery studied *Vaccinium myrtillus,* and found that it lowered the concentration of sugar in urine but *not* in blood.

Finally, in Jassy, Dr. C. Bart, and in Athens, Dr. Emmanuel made studies of *Morus nigra,* and in their conclusions they agreed in establishing the reputation of this drug as an antidiabetic.

A careful survey of the literature having failed to disclose any pharmacological and clinical investigations of *Momordica charantia,* and there being little chemical data available, it was decided to study the chemistry of the drug, its toxicity and pharmacological effect on rabbits, and its effect on mildly diabetic patients. From this study there is already evidence at hand that the drug possesses at least some hypoglycemic action on rabbits; this fact, together with the encouraging results obtained in a diabetic case study at Hahnemann Hospital and the excellent reputation of the drug in Puerto Rico, suggested publication of a preliminary report of the investigation thus far. It is to be strongly emphasized, however, that the work has not reached the point where definite assurance can be given that the drug possesses insulin-like properties.

This report presents the following: (1) History of the drug; (2) botanical descriptions and preliminary histological studies; (3) chemical studies; (4) the effect of the drug on the blood sugar of rabbits; (5) clinical findings.

History and Empirical Uses of the Vine

Momordica charantia is a native of Tropical Asia and Africa. Probably the vine was taken to Puerto Rico by the slaves. We have

not been able to trace its origin in the island, nor when the natives started using it as an antidiabetic, nevertheless, it has been used as such for fifty years, at least. The description of the plant is very confusing, because of the similarity of *M. charantia* to *M. muricata, M. cylindrica, M. balsamina, M. zeylanica,* and *M. ch. abbreviata.* In the tropics the same *M. charantia* runs into many forms.

The first written information of the vines appeared in 1813 when Ainslie (2) mentioned its use as a pot-vegetable. In 1826 the same author (3) mentioned the medicinal uses of the vine in the treatment of bleeding piles, in certain bowel affections, and in curing wounds. In Jamaica, Ainslie quoted, "The natives used boiled leaves as well as a decoction of the plant itself, equally, to promote the lochiae."

In 1891 Dymock (4) gave a complete description of the plant and its uses, stating it to be a kind of panacea for use in scabies, leprosy and other cutaneous diseases. Fruit and leaves have been used also as anthelmintic, emetic, purgative, in bilious affection, in night blindness, tonic stomachic, anti-rheumatic, in gout, and in diseases of the spleen and liver.

In 1894 Bailey (5) mentioned the use of the rind in medicine. In Batvia (1898) Peckolt (6) discovered an alkaloid in the vine and described the use of the vine as an anthelmintic, purgative and emetic, and in 1904 he (7) verified the discovery of the alkaloid and called it Momordicin. Other uses of the plant are given in his paper.

In 1929 Freise (8) described the use of the emulsion of the seed as an anthelmintic by the Brazilians.

In the Philippine Islands, Tavera (9) described the uses of the plant in medicine.

In Cuba the plant is used in curing wounds which are refractive to other kinds of treatment, in cutaneous diseases, and for sterile women.

In the Dominican Republic, under the name "Sorrosie," the vine is used as an anti-diabetic.

In South America the plant is not mentioned at all in the book "Medicinal Plants" by Dr. Arroyo, nor in the book of Delchi.

In Puerto Rico in 1936, Torres Diaz (10) started a preliminary investigation of the alkaloid, and verified the presence of the alkaloid discovered by Peckolt in 1898. Diaz also mentions the use of the plant in the treatment of diabetes.

The vine is also used in the island in the treatment of scabies in animals, for parasites of the head in children, and on the scalp. One yard of the vine boiled in one liter of water, and the infusion taken three times a day, is used for antimalaric effect.

The vine is likewise well known as a drug for the treatment of chronic ulcers of the stomach.

Botanical Description of Momordica Charantia L.

The genus *Momordica* (Momordi, from mordeo, meaning to bite (for the seeds appear to have been bitten)), belongs to the order Campanulales, family *Cucurbitaceae* or "gourd family." They are herbaceous, climbing or prostrate vines, with simple or forked tendrils and dioecious or monoecious, mostly yellow, flowers; the staminate is solitary or clustered, the pistillate is solitary. The staminate flowers have a five-lobed calyx, a nearly rotate five-parted corolla and usually three stamens with short filaments, borne at the calyx mouth, the anther sacs are flexuous. The pistillate flowers have a calyx and corolla like those of the staminate, a one-celled ovary with three placentae; the numerous ovules are horizontal, the style slender, and there are three stigma. The fruit is ovoid to cylindric, three-valved or indehiscent. The name is of Latin origin but of uncertain meaning. There are about twenty-five species in this genus, all from the tropics.

PLATE No. 1. Photoscopy of Plate No. XLVI. (*Momordica Charantia L.*) Presented by O. F. Cook and G. N. Collins in Economic Plants of Porto Rico. Contr. Not Herbarium 8 (2); 57-269 (1903).

In Puerto Rico there are only two species of *Momordica:* the "balsam apple," *M. balsamina L.*, which is occasionally

planted as an ornamental plant, and the "wild balsam apple," *M. charantia L.,* which is widely distributed in the Island from seashore to high altitudes. The latter is most abundant at lower altitudes in fields, thickets, hedges and waste grounds, and is known locally as "cundeamor." Its fruit is not edible, but is extensively used in feeding cage birds.

There has been some controversy about the classification of *M. charantia* by botanists (Cook and Collins, Sintenesis, Urban and Britton and Wilson (11), (12), (13). Some of them claimed that there are two species, *M. charantia L.* and *M. zeylanica Mill.,* but Britton and Wilson placed both as one species, *M. charantia L.*

Since the "Descriptive Flora of Puerto Rico" by Britton and Wilson is the most recent and extensive revision of the flora of the island, we feel justified in following it. The description here is as follows:

"Momordica charantia

Stem slender, more or less pubescent, 1-8 mm. long, with simple filiform tendrils, opposite the leaves. Leaves thin, reniform or suborbicular in outline, 4-12 cm. broad, deeply pedately 5-7 lobed, glabrate or pubescent, the lobes dentate, acute or obtuse, the slender petioles 3-6 cm. long; peduncles of the staminate flowers with an ovate entire cordate bract at or below the middle; sepals oval or ovate 3-4.5 mm. long; corolla-segments obtuse or emarginate, 1.5-2 cm. long, yellow; fruit orange-yellow, tuberculed, 2-12 cm. long; seeds flat, 12-16 mm. long, creamy color, embedded in a bright red, soft aril, with a sweetish taste."

Other botanical descriptions are given by Drury, (4) Bailey, (14) Small, (15) and Torrey, (16). Plates 1, 2 and 3 represent photographs of the vine and its parts.

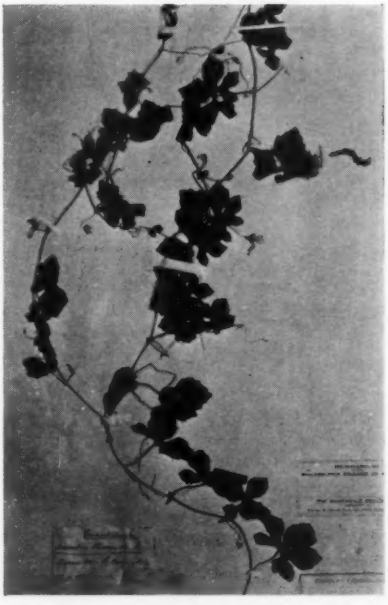


PLATE No. 2. Vines of *Momordica charantia.* (Courtesy of the Philadelphia College of Pharmacy and Science, Martindale Herbarium.)

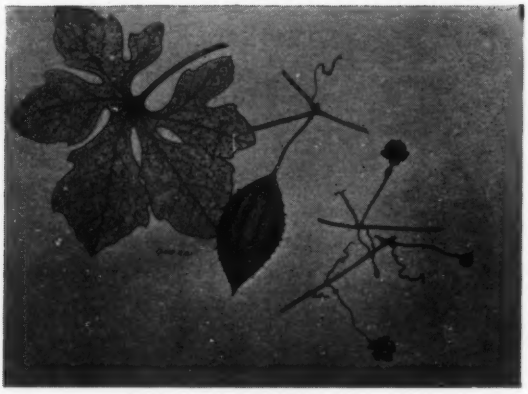


PLATE No. 3. Photograph of a Drawing of the Plant Presented by Mr. Roena. Showing a leaf, tendrils, male and female flowers.

Preliminary Histological Description of a Leaf

On April 16, 1940, specimens of leaves of *Momordica charantia L.* were sent to the author from the experimental station by J. I. Otero, a Puerto Rican botanist. According to Solereder (17) no comprehensive investigation of the leaf structure of *Momordicas* has yet been done. The author, with the co-operation of Dr. Marin Dunn,

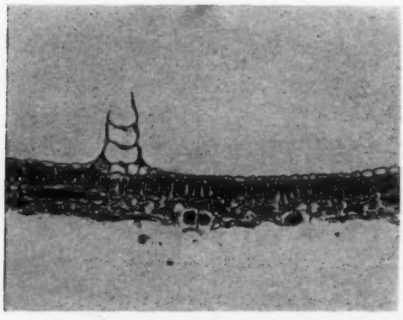


PLATE No. 4. A transverse section of leaf of *Momordica charantia L.*, showing a hair and cystoliths.

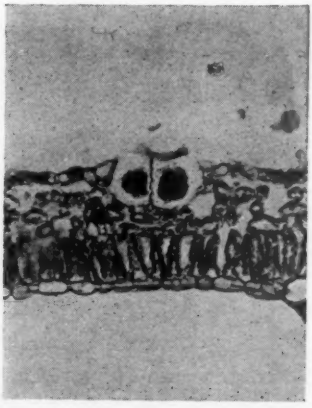


PLATE No. 5. Enlarged portion of Plate No. 4, showing double cystoliths.

Head, Department of Biology, decided to make at least a preliminary observation of the specimens received. It is expected that the botanical study of this plant will be carried on in the near future by Mr. E. W. Martin, under the direction of Dr. Dunn.

A number of cross sections of the leaves were done and slides prepared according to the technique of Chamberlain (18).

As may be seen from Plate No. 4, a transverse section of the leaf of *Momordica charantia* shows the following well-defined regions: (a) an upper epidermis from which in places arise large, multicellular, uniseriate hairs; (b) one layer of elongated chloroplastid containing palisade cells under the epidermis; (c) a zone of spongy parenchyma composed of 3-5 layers of irregular chlorophyll bearing cells with prominent intercellular spaces and now and again a small fibro vascular bundle; (d) a lower epidermis which is here and there provided with stomata.

Our study confirms the observation of Penzig (17) that associated with the lower epidermis are true double cystoliths (see Plate No. 5)—the epidermal cells containing them penetrating the overlying spongy parenchyma for a considerable distance. Double cystoliths are rarely found in *Momordica charantia* according to Solereder (17). In our specimen they are present.

Summary of the Chemical Studies

Samples of the entire plants were collected in various places in the island. The wet material was sent to the School of Tropical Medicine, weighed, dried in a Freas electric hot air oven at 35°-40° C., and again weighed. The dried material was then ground in a Wiley mill, collected in air-tight cans and shipped to the college. From this material a representative sample was prepared and analyzed according to A. O. A. C. methods.(19) The total phosphorus was determined colorimetrically by a modification of the Bell-Doisy method.(20) A comparative study of the chemical composition of the different parts of the plant was also made, and results are presented in Table I.

TABLE I

CHEMICAL COMPOSITION OF THE PLANT

DRY BASIS EXCEPT ANALYSES MARKED *

No. Sample	Name of the Material	Total Solids %	Crude Protein N x 6.25	Ether Soluble Extract	Alcohol Soluble Extract	Crude Fiber %	Carbohydrates %	Ash %	Ca %	P. %
1	M. ch. Root		9.25	2.17	17.84	48.53	33.33	6.72	0.709	0.292
2	M. ch. Stem		8.38	1.42	11.26	53.08	30.73	6.39	0.546	0.198
3	M. ch. Leaves		21.19	4.03	22.83	13.79	44.05	16.94	4.393	0.315
4	M. ch, Green Fruit	*10.25	20.69	4.26	22.01	25.78	40.70	8.57	0.299	0.168
5	M. ch. Whole Plant (dried 45° C. oven)		20.06	3.26	21.13	23.54	39.15	13.99	3.01	0.301
6	M. ch. Whole Plant (sun-dried)		18.56	2.79	24.40	27.85	36.95	13.85	2.68	0.310
7	M. ch. Whole Plant 1939 Sample	*12.26	20.69	4.04	22.30	25.64	35.60	14.03	1.23	0.441

Attention is called to the relatively high content of crude protein, mineral matter and calcium, as compared with other plants of the flora of Puerto Rico.

Extraction With Various Solvents

A study of the effect of various solvents applied by maceration according to Lyons' methods (23) and by continuous extraction in the Soxhlet apparatus yielded the data shown in Table II (Powder No. 80 used):

TABLE II

Solvent	Maceration per cent.	Soxhlet per cent.
Ether U. S. P.	4.12	5.48
Chloroform U. S. P.	4.00	7.92
Boiling Water	20.61	...
2% Sulfuric Acid	51.20	...
1% Citric Acid (Boiling)	30.35	...
Petroleum Ether 45°-60° C.	2.24	2.34
Petroleum Ether 25°-40° C.	2.00	2.28
Acetone U. S. P.	4.50	5.53
Alcohol 95%	20.00	22.30
Benzene U. S. P.	4.00	5.77

Comparative Soxhlet extractions with different solvents were also made. The volatile portions were recorded in those solvents of low boiling point. Results are set forth in Table III.

TABLE III

Comparative Extractions

	Solvent and Specification of Purity.	Total Soluble Extract Vacuum Dried Per Cent.	Volatile Portion of S. Extract Per Cent.
1	Carbon Tetrachloride Absolute	3.41	15.19
2	Carbon Tetrachloride Commercial	3.92	15.15
3	Carbon Bisulphide Absolute	3.12	15.00
4	Petroleum Ether 20°-40° C.	2.53	44.81

TABLE III—Continued.

Comparative Extractions

	Solvent and Specification of Purity.	Total Soluble Extract Vacuum Dried Per Cent.	Volatile Portion of S. Extract Per Cent.
5	Petroleum Ether 30°-80° C.	2.65	33.66
6	Methylene Chloride Reagent	5.88	
7	Acetone Absolute	12.42	
8	Acetone U. S. P.	5.53	
9	Ether Commercial	6.71	6.15
10	Ether U. S. P.	5.41	7.12
11	Ether Absolute	3.22	7.15
12	Isopropyl Ether	5.62	
13	Chloroform Absolute	8.78	
14	Chloroform U. S. P.	7.92	
15	Ethyl Acetate Absolute	10.17	
16	Benzene Absolute	8.08	
17	Benzene U. S. P.	5.77	
18	Methyl Alcohol U. S. P.	23.00	
19	Ethyl Alcohol U. S. P.	25.00	
20	Propyl Alcohol C. P.	21.45	
21	Butyl Alcohol C. P.	18.05	
22	Amyl Alcohol	20.90	

A sample of the drug was sieved fractionally and separated into fractions of powder No. 40, No. 60, and No. 80. A portion of each fraction was extracted in a Soxhlet apparatus with Ethyl Ether U. S. P. to exhaustion (22 hours) and the total ether-soluble extractive and volatile ether-soluble extractive determined as directed in U. S. P. XI.(24) The results are set forth in Table IV.

TABLE IV

Variation of Ether-Extractive With Degree of Comminution

Powder No.	Air Dry Moisture	Total Ether-Soluble Extractive	Volatile Ether-Soluble Extractive
40	8.02%	4.36%	2.06%
60	9.14%	4.78%	2.20%
80	9.91%	5.48%	2.55%

Attention is called to the increase of total extractive as the particle size of the powder decreases.

For the subsequent systematic process of analysis of the plants, powder No. 80 was used, and analyzed as recommended by Dragendorff (21) and Rosenthaler (22).

The principle of the method of Dragendorff consists in the treatment of the powdered material with a series of different solvents in succession. This involves extraction by macerating the powder and menstruum (1:10) for eight days. The following menstruua were used: Petroleum spirit, ethyl ether, ethyl alcohol, distilled water, dilute caustic soda, and dilute hydrochloric acid. In addition, a comparative study of this maceration method with procedures employing a Soxhlet and a continuous percolation apparatus was performed in order to determine to what extent the exhaustion of the drug depended on the method of extraction. The results were as follows:

TABLE V

Method of Extraction	Petr. Ether %	Ether %	Alcohol %	H_2O %	NaOH %	HCl %
Maceration, for 8 days, 30 Gm. drug	0.63	2.12	4.38	17.60	7.56	8.27
Soxhlet extractor, 5 Gm.	1.71	3.59	12.15	...	...	...
Continuous Percolation, 300 Gm.	1.86	3.33	13.70	...	...	...

The continuous percolation of 300 Gm. of drug was carried out in an apparatus, constructed in this laboratory, similar to Wester's extraction apparatus, with the exception that a percolator was used instead of an aspirator bottle. This worked very rapidly and could be operated continuously without constant attention.

Examination of Extractive Portions

Petroleum Ether Extractive

Thirty grams of No. 80 powder was transferred to a narrow, glass-stoppered 500 cc. cylinder, macerated with 300 cc. of petroleum ether (25°-40° C.) for eight days, shaking several times daily, then filtered. The color of the extract was yellow and it yielded 2.0 per

cent. of total solids (referred to the air-dried drug) of which 30 to 40 per cent. is a volatile highly aromatic ethereal oil, as determined by the Osse technique. The latter is not a method of high accuracy but does merit some analytical consideration. In the non-volatile residue, which was appreciably soluble in absolute alcohol, the presence of a fixed oil was established on the basis of a positive test for glycerin (by the dihydroxyacetone test of Hass (25). Free fatty acids (detected by rosaniline), cholesterin (indicated by the sulfuric acid and the ferric chloride-hydrochloric acid tests), and carotene were found. Mayer's reagent did not yield a positive test. Under the microscope the non-volatile residue showed highly refracting globules dispersed throughout with red, chloroform-soluble rods (identified as carotene) also present. No granules of chlorophyll were observed. This fat-like substance was isolated from the seeds of *Momordica charantia* by Corfield and Caird (26). Further work was done on it by Toyama (27) and Yozaki (28).

Ethyl Ether Extractive

Following exhaustion of the drug with petroleum ether, the dried residue was macerated with ethyl ether for eight days, filtered and diluted to a definite volume. This extract yielded 2.12 per cent. of total solids, 1.99 per cent. being non-volatile and 0.13 per cent. volatile (all figures referred to air-dried drug). Chlorophyll was present in large amount in this extract. Application of the Sachsse (10) technique for separation of pigment yielded cyanophyll or phylocyanin (blue, soluble in ether and benzene) and xanthophyll or phylloxanthin (yellow, insoluble in ether and benzene); these tests conclusively proved the presence of chlorophyll.

Evaporation of a 200 cc. portion of ethereal extract yielded a residue of 0.508 gram of which (a) 7.04 per cent. was soluble in water; (b) 85.10 per cent. was soluble in 95 per cent. alcohol, and (c) the remainder, corresponding to 7.86 per cent., was insoluble in both. This latter portion was designated as indifferent resin or resin anhydride. Qualitative tests on these portions are now described.

The water soluble portion (a) is colorless, highly aromatic and bitter. Tests for gallic acid, salicylic acid, salicin and benzoic acid were negative; benzoic acid had been reported to be present in other Momordicas. Extraction of an acidified portion of (a) yielded a glucoside which, in several qualitative tests, showed great similarity to

elaterin. Extraction of an alkalinized portion of (a) yielded traces of an alkaloid of very bitter taste and with a pungent odor. This turned yellow with concentrated sulfuric acid.

In portion (b), which is soluble in alcohol, an acid resin was obtained. This portion has been reserved for further studies.

Portion (c), called inactive resin by Dragendorff, was insoluble in water, in acidified water and in alcohol, and produced an intense green color with concentrated sulfuric acid, as well as with a mixture of sulfuric acid and sugar; no reaction was observed with bromine water; fuming nitric acid oxidized most of it with development of an intense red color, though traces of the resin were not dissolved. This inactive resin, upon hydrolysis with alcoholic potassium hydroxide, gave a crystalline substance, insoluble in ether and in alcohol. This substance was recrystallized from water and again warmed with alcoholic potassium hydroxide, whereupon a transient carmine color was developed; on cooling the color disappeared.

Examination of the Alcoholic Extractive

Alcoholic maceration of the exhausted drug from the ethyl ether extraction yielded total solids amounting to 4.38 per cent., of which 18.25 per cent. was mineral matter. Of the total solids 37.6 per cent. was soluble in water, 36.6 per cent. was soluble in ammonia (1:50), the remaining 25.8 per cent. was indifferent resin (Dragendorff).

The portion soluble in ammonia water was acidified with acetic acid and the weight of precipitate calculated as phlobaphene. The yellow filtrate was alkalinized, extracted with chloroform and the chloroform residue dissolved in 2 per cent. sulfuric acid; this solution gave a precipitate with Mayer's reagent.

The portion soluble in water was negative to tannin by the ferric chloride test. A portion of a few cc. of this solution was precipitated with lead acetate and filtered; this filtrate was negative for glucose. The precipitate was washed into a beaker with water, boiled with sulfuric acid, filtered to remove lead sulfate, and the filtrate tested for reducing sugar. This test was positive, indicating a glucoside.

The presence of glucoside was confirmed as follows: Two 10 cc. portions of the aqueous solution were precipitated with lead acetate and copper acetate respectively, each precipitate was collected in a Gooch crucible, ignited and weighed, then by deducting the weight of

the organic matter (loss in weight) contained in the copper precipitate from that contained in the lead, the weight of the glucoside was obtained. A difference in weight of 2.6 mgm. was obtained. However, this is not to be considered a quantitative determination; rather it is an indication that some glucoside is present.

The rest of the water soluble portion of the alcoholic extractive was extracted by agitation with solvents. The glucoside mentioned above was found to be highly aromatic, and gave with concentrated sulfuric acid a cherry-wine color. A trace of an alkaloid was noted also; this with concentrated sulfuric acid yielded a canary-yellow color.

The precipitate has been recrystallized and is now being investigated for possible hypoglycemic action on rabbits. This phase of the work will be reported on later.

Examination of Substances Soluble in Water

Aqueous maceration of the drug previously exhausted with alcohol yielded a liquid which is very bitter, turbid and, when shaken, produces a honey comb-like froth. The total solids residue varied from 17.0 per cent. to 17.6 per cent. on various samples. Of this, 53.7 per cent. was mineral matter.

The aqueous extract upon mixing with two volumes of absolute ethyl alcohol yielded a precipitate of mucilaginous substances (3.6 per cent.) which reduced Fehling's solution after hydrolysis. The filtrate, after precipitation of the mucilaginous substance, is clear and canary yellow in color. No alkaloid was found to be present. The filtrate reduced Fehling's solution immediately.

The aqueous extract (equivalent to 5 grams of drug) upon precipitation with basic lead acetate yielded 0.202 gram of organic matter; 0.137 gram with neutral lead acetate; 0.097 gram with copper acetate. On reduction with Fehling's solution 0.003 gm. of Cu_2O was obtained; after hydrolysis with hydrochloric acid 0.021 gm. of Cu_2O was obtained; this increase may be due to hydrolysis of the mucilaginous substances.

On the bitter yellow residue obtained from the filtrate of the aqueous extract which had been mixed with alcohol, the following tests were made:

A—with concentrated sulfuric acid it gave a red color and developed an aromatic odor. On dilution with water a precipitate was formed.

B—with concentrated hydrochloric acid a yellow color resulted.

C—with concentrated nitric acid a cherry-wine color, which persisted on dilution with water, was produced.

D—with ferric chloride and hydrochloric acid it gave a red color, as with sulfuric acid, but changed to greenish yellow on dilution with water.

E—it is slightly acid in nature.

The bitter yellow residue was hydrolyzed with sulfuric acid and diluted with water. The ether extract of this solution, upon evaporation, gave an aromatic residue.

In the water-soluble portion of the drug a saponin-like substance was observed to be present. Negative hemolytic tests were obtained; nevertheless several qualitative tests were positive for saponin. The saponin was hydrolyzed by concentrated sulfuric acid forming a sapogenin which is insoluble and was removed by filtration. The filtrate reduced Fehling's solution. Further studies of this saponin-like substance will be done later.

Summary

A preliminary chemical investigation of the drug *Momordica charantia L.*, used empirically in Puerto Rico for the treatment of diabetes mellitus, has been made. Among the findings reported are the following:

1. Determinations of total solids, ether-soluble extract, alcohol soluble extract, crude protein, crude fiber, carbohydrates, ash, calcium and phosphorus in the roots, stems, leaves and green fruit of the plant, as well as in the whole plant itself.
2. Data on the amounts of extractive removed by various solvents and the influence of particle size on the amount of extractive.
3. Results of the application of Dragendorff's method of successive extractions of the drug with petroleum ether, ethyl ether, alcohol, and water.

These data indicate: (a) that the petroleum ether extractive includes a highly aromatic ethereal oil, a fixed oil, traces of free fatty

acids, and carotene; (b) that the ethyl ether portion contains chlorophyll, a glucoside-like substance and resin; (c) that the alcohol fraction contains alkaloid (probably two, one of which is Momordicin—for details, see thesis); a glucoside-like substance and a crystalline substance of unknown nature which is being investigated further; (d) that the water-soluble extractive includes a saponin-like substance and mucilaginous bodies.

Acknowledgments

Appreciation is expressed to the following for their help in connection with this work: Dr. Ivor Griffith and Dr. Arthur Osol, of the P. C. P. & S., for their advice and supervision; Dr. G. Bachman, Director of the School of Tropical Medicine of Puerto Rico, for arranging for this work; Dr. J. H. Axtmayer, of the Department of Chemistry of the School of Tropical Medicine, for the preparation of the samples; Mr. L. J. Kleckner, for assistance in certain microscopical examinations; Dr. M. S. Dunn, for the histological study of the leaves; Miss C. L. Graff, for compilation of bibliography; Mr. J. I. Otero, for botanical data on Momordica; and Mr. E. W. Martin, for photographic work.

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OUR CONTRIBUTORS THIS MONTH

Arthur Osol, Ph. D., is director of the chemical laboratories and Assistant Dean of Science of the Philadelphia College of Pharmacy and Science. Well known in American Pharmacy for his frequent scientific contributions, he is also on the editorial staff of the *American Druggist.*

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BRITISH PHARMACY CARRIES ON

Following is a letter from a British correspondent, owner of three chemist shops in London, revealing the innermost thoughts of a pharmacist under fire. After reading the message, we fortunate pharmacists of America can sympathize even more with our professional contemporaries all over Europe who are carrying on so nobly under such dreadful handicaps.

I AM afraid that each of my pharmacies is war scarred. Last summer proved quite exciting, although lifting and sorting one's dispensary from off the floor began to become not so amusing. It is amazing, however, to discover the relatively small amount of damage that can be behind a picture of ruin. Blast is a fearful, horrible thing, yet it sometimes passes one by, almost delicately! My main discovery is the source of that evasive odour always connected by folk with 'real' pharmacies. When umpteen volatile oils, as many galenicals, and a sprinkling of chemicals blend after a five foot leap to the floor, I guess I was at the smells' point of origin!!

I have heard tell, that the 'Multiples' have been advertising for some of this smell in order to spray their shops with 'atmosphere'. Pharmacies here have taken on a rather old fashioned appearance that is intriguing. Farewell glass! Boarded fronts are the thing, a small space being left glazed, usually sufficient to display a carboy. The effects are quaint and pleasing, artistry helping to achieve the most attractive results, and so folks carry on. My shelves now carry their bottles behind lengths of string, so discouraging dancing at night to the very vibrant music of bombs and guns. Often do I find, on arrival in the morning, my bottles looking very much drunk, but not since the stringing,—over the 'top'. This has saved me many now rare drugs.

Pharmacy is experiencing a number of interesting events, which I think most promissory. For instance, the limitations imposed upon luxury articles is threatening the existance of many high priced but useless toilet articles, and driving the public to the skill of the pharmacist to substitute from the bottles in his shelves. Millions of pounds spent in making women cosmetic conscious to the tune of

Miss Ardys epidermal pulchrifiers, or Miss Rubies new lip approach, are now slipping their hold, and are giving place to a growing sophistication in the public mind regarding toilet and beauty preps. A respect is growing for the pharmacist, for he can now make Mrs. Smith her very indispensable vanishing cream, and the dear lady realizes that it is not only as good, but so much cheaper! Whether this respect is due to our pharmacist being the sole source of supply, or to his capability I do not know, but I can but hope. . . .

This sophistication has also spread to the medical sphere, and the metamorphosis is most pleasing. Many agencies for foreign patent medicines are watching their advertising investments disappearing, as further supplies are impossible. Scarcity and economy are forcing common sense measures, and drugs rather than patented fancy names are being prescribed. This is becoming more and more the case, and the doctors, like the ladies, are realizing how much they were gullible victims of advertising, and sales talk. The aspect, as I said, is good, and points to pharmacy being on the road to a real and stable status, and the pharmacist taking onto his shoulders the dignity of Ye Old & Ancient Apothecary, tho I hope with more scientific a right.

I have only just done an hour's work with my brother, who sits for his M. P. S. in June. It is difficult to picture these youngsters on such a syllabus, putting up with the cheap quackery of prewar Pharmacy. I am certain they will better things. It may interest you to know that it was as a result of a short soliloquy out in the garden, that prompted me to sit down now and write to you.

We had been working steadily in silence, although an alert had been sounded, but the shooting had come very close, and the drone of engines too uncomfortably overhead. We decided under the circumstances that Poison Law could be spelt with small letters, and went in to the garden where we have a concrete sub-surface shelter. However I did not take cover, but watched the dark night being shattered by the roar and flashes of guns and the small red spots of shells bursting in the sky. Searchlights used to make the most wonderful pictures, but they do not seem so popular now. Thrilling too, when by their travel they told not only that Jerry was coming, but that the devils were right overhead.

When things had become quieter, my brother went on with his work, and I just sat down at the machine to write this. The All

Clear sounded some minutes back and seems to have snapped my feeling to write. This raiding is more exhausting when it is a little distance away, than when it is round about. There is nothing one can do but listen to the bombs shishing down on their filthy errand, helpless. It can be awe inspiring, this terrific fight between an invisible city and an invisible bomber. When there is a moon to silver and beautify everything, one can be bitter and angry with man, but in the black dark night, there is something satanic about it all that seems to bring the worst out in one.

The most astounding thing about this war, is the refusal of the people here to be worried or flurried. Conversation is perhaps more political, naturally, but otherwise normal. Bomb talk is considered boring, and sport is still the prime interest in life. Of course getting Hitler is also now the national pastime like cricket, and rely on it England will get his ashes as the Australians are getting Musos. There is very little bitterness, all things considered, and folk are steady, with an utterly complete faith in the final result. I can even visualize folk here holding protest meetings to stop the government giving Germany what she is trying to do to our cities and towns.

Well, here I am still writing. Not much left for sleep now. I do hope this letter reaches you.

My Compliments and regards.

Yours very sincerely,

NATHAN ZAMET.

BOOK REVIEW

A Candid Opinion of a New Volume

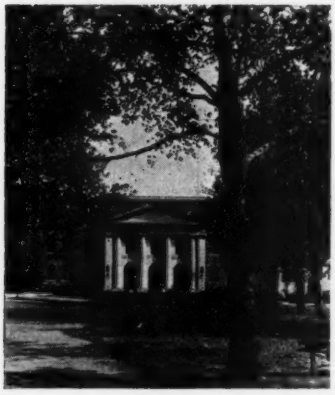
Medical Manual of Chemical Warfare. Reprinted by permission of The Controller of His Britannic Majesty's Stationery Office. First American Edition, Chemical Publishing Company, Inc., 234 King Street, Brooklyn, N. Y., 1941. 119 pages, 11 plates. Price: $2.50.

Although this book provides mostly information about the physiological effects of chemical warfare agents and the treatment of casualties produced by these agents, it presents also a wealth of information concerning the physical and chemical properties, and methods of dispersion, of such substances. The nine chapters of the book deal with the general aspects of gas warfare, the vesicant gases, the lung irritant gases, paralysant gases, harassing agents, arseniuretted hydrogen poisoning, dangerous gases not used for offensive purposes, protection against gas and air raids, and the recognition and first aid treatment of gas casualties. Three appendices provide: (1) A summary of gases, their properties, methods of recognition and first aid treatment; (2) methods for the administration of oxygen; (3) an atlas, with ten plates, on the effects of phosgene and mustard gas poisoning.

The book is of value not only to medical officers of the defense services, but to chemical officers and others engaged or interested in chemical warfare.

ARTHUR OSOL.

PHILADELPHIA COLLEGE OF PHARMACY AND SCIENCE HOLDS 119th ANNUAL COMMENCEMENT



On June 4, 1941, the Philadelphia College of Pharmacy and Science awarded four honorary degrees and 76 degrees in course. The address was delivered by Dr. Reuben T. Shaw, past president of the National Education Association and head of the science department of the Northeast High School, Philadelphia.

The following were the recipients of the degrees:

Doctor of Science (*Honoris Causa*)

C. P. Dubbs — Victor Oliver Homerberg

Master of Pharmacy (*Honoris Causa*)

Frank T. Gillespie — Herma Alice Rohn

Doctor of Science in Bacteriology

David Perlstein

Doctor of Science in Pharmacy

Gilberto Rivera Hernandez

Master of Science in Bacteriology

Vera E. Milanick

Master of Science in Chemistry

Samuel L. Ross

Master of Science in Pharmacy

Eugene L. Cohen — Harry T. Rubino
Edwin A. Mandel — Norman H. Shull
Chamlong Suvagondha

Bachelor of Science in Chemistry

Maxwell Gordon — Martin Sackoff
Harold Marcus — Richard N. Selvig
Sidney Melamed — William A. Sieber
Frank W. Volz

Bachelor of Science in Bacteriology

Henry S. Burlington — Albert Levitan
Joseph J. John — Forrest N. Magee
Simon E. Levin — Thomas W. Mou

Bachelor of Science in Biology

Albert S. Kaplan — Leonard Teitell
Donald W. Mayer — Jane L. Weygandt

Bachelor of Science in Pharmacy

Jacob Alpern
Sister Maria Aupperle
Lewis H. Berk
Morris Blatman
Joseph Blum
Harvey J. Breeding
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